not been established, they may be pertinent to the mechanisms of both tissue deposition and glomerular clearance of urate. We have studied plasma urate binding by a method of equilibrium dialysis. In this method aliquots of freshly obtained plasma were dialysed for 16 hrs at 4°C. against large volumes of 0.01 M phosphate buffer containing 15 mg. uric acid per 100 ml. buffer. After equilibration, the amount of uric acid within the dialysis bag in excess of that in the buffer was considered to be bound. The quantity of urate bound is dependent on the free urate concentration, the temperature, pH, and molarity of the buffer, and the protein concentration of the plasma. Other factors which appear to affect urate binding have also been studied in detail. Ingestion of aspirin, probenecid, and phenylbutazone impaired urate binding. The mechanisms of this impairment was studied *in vitro* using human albumin and dye displacement techniques. Likewise, very low plasma albumin levels resulted in a complete loss of urate binding capacity. Lastly, three patients with severe tophaceous gout had grossly impaired urate binding.

Discussion

DR. H. L. F. CURREY (*London*) I was trying to estimate the significance of this binding in terms of the actual percentage of urate in the plasma which might be bound. Am I right in thinking that if, in what you describe as the optimal conditions in your system, 30 µg./ml. urate is bound, this would suggest that about 2 per cent. of the urate might be bound *in vivo*? If one thinks that non-bound urate is the factor in the plasma which determines crystallization in the tissues, this would seem a very marginal and small influence even under the best conditions. I can understand this competitive binding might be important in the opposite direction in terms of the influence on drugs, but I am surprised that you place so much significance on altering the concentration of unbound urate by as little as 2 per cent. [Correctly calculated = 20 per cent.]

DR. BLUESTONE An estimate of the amount that might be bound in the physiological state *in vivo* was made by Dr. J. R. Klinenberg long before I joined him. From the relationship between bound urate and the concentration of urate *in vitro*, it was estimated that about 15 to 20 per cent. of the uric acid of a serum urate of 8 mg. per cent. could be bound; but of course this is partly guesswork and you cannot necessarily extrapolate direct from the state *in vitro* to that *in vivo*. This is where we are in grave difficulties because no one has yet thought of an unequivocal method of demonstrating urate binding *in vivo*.

PROF. E. G. L. BYWATERS (*Taplow*) Has anyone examined the interstitial or oedema fluid? This has a very low content, under 0.1 per cent., of protein and should reflect this binding and non-binding.

DR. BLUESTONE No, that would be very helpful, but I am not aware that it has been done. One idea was that we might study the renal tubular fluid by the micro-puncture technique in a rat with chemically-induced hyperuricaemia in order to study urate binding in that situation, and this is the basis of a scheme we are now considering.

DR. J. T. SCOTT (*London*) This is interesting and important work, but I agree with Dr. Currey that one

must be careful about some of the inferences that have been drawn. For example, it is unlikely that alteration in binding plays a significant part in the acute gout which sometimes follows the start of treatment, since you have shown that allopurinol, which tends to produce acute gout even more than uricosuric drugs, has no effect on urate-binding.

DR. BLUESTONE We absolutely agree, and there is no direct correlation between our experiments *in vitro* and the clinical situation. Nevertheless we might be throwing light on some factors that apply in some circumstances.

DR. A. S. RUSSELL (*Taplow*) In one of your latter Tables, when you were talking about the analogy with DNSA binding, I am a little confused as to the relative potencies of the different drugs. As I remember, indomethacin is the most effective in displacing DNSA—

DR. BLUESTONE The second most effective—

DR. A. S. RUSSELL (*Taplow*) And yet it did not figure in the uric acid displacement?

DR. BLUESTONE Yes; this is because when we give indomethacin to patients or to normal subjects the plasma concentrations obtained are very low. You get nowhere near the 0.2/0.3 millimolar levels we have in our system *in vitro*. The fact that phenylbutazone was so high up on the DNSA displacement table indicates that we have probably mapped out a specific binding site for that drug.

DR. A. S. RUSSELL (*Taplow*) What did you think about the urate binding reported by Kelley in the alpha₂ globulin region? Did you do any studies putting just albumin in your dialysis bags or something of this sort?

DR. BLUESTONE Yes. The experiment we did *in vitro* was one with purified albumin. Coming back to the alpha₂ globulin work, the whole year apart from this work was spent trying to confirm those findings and resulted in miserable failure. We could not demonstrate any significant urate-binding protein which lay outside the albumin/pre-albumin range, at least in terms of electrophysical properties.

DR. A. ST. J. DIXON (*Bath*) Neither the speaker nor the discussers seem to have mentioned the problem of the rate of urate-unbinding. What matters physiologically is not the equilibrium state so much as what happens when you change it. Supposing in your experiment you remove the 15 mg. per cent. urate from the surroundings, how soon does the urate which is bound to protein uncouple and become free again? This is important in considering the clearance of urate through the glomerulus.

DR. BLUESTONE The answer is, instantly. One of the things I tried to emphasize earlier is that the bond between protein and urate is a remarkably weak one and has foiled investigators for many years. Unless you provide a surrounding medium of free excess urate, the bond simply uncouples.

Sjögren's Syndrome in an Ophthalmic Milieu. By J. M. GUMPEL and P. WRIGHT (*Royal Postgraduate Medical School and Moorfields Eye Hospital*)

Since Sjögren drew attention to the association of joint disease and kerato-conjunctivitis sicca (KCS), this syn-

drome has attracted considerable attention, but most of this work has concerned patients seen because of rheumatic complaints.

This study surveys a group of patients with KCS as the index symptom attending a special clinic at Moorfields Hospital, and establishes the prevalence of rheumatoid arthritis and other connective tissue diseases, in comparison with a matched control group. 'Auto-immunological' activity was studied.

Of the 65 patients surveyed, 23 had rheumatoid arthritis, 24 had xerostomia or parotid swelling without evidence of other connective tissue disease, four had progressive systemic sclerosis or variants thereof, and in fourteen the KCS was the sole manifestation.

Autoantibodies were found in a remarkably high number of patients, especially antinuclear factor, comparable to series with more systemic involvement, but rheumatoid factor was less common. Immunoglobulin levels were considerably raised. Antibody against salivary gland duct epithelium was also found mainly in the rheumatoid subjects but was seemingly unrelated to overt parotid involvement.

Discussion

DR. A. K. THOULD (*Truro*) What thyroid disorders did you find in your patients with rheumatoid arthritis and Sjögren's syndrome?

DR. GUMPEL Ordinary uncomplicated goitre without thyrotoxicosis or myxoedema.

DR. A. K. THOULD (*Truro*) No evidence of a thyroiditis for instance?

DR. GUMPEL No. The results for thyroid antibodies as gauged by a thyroid microsomal antibody were not higher in these patients than in any of the others.

DR. W. W. BUCHANAN (*Glasgow*) I was particularly interested in the group of patients with KCS, because, as you say, no one has made a systematic study of these patients. From your observations it would appear that they have a mild degree of Sjögren's syndrome. Have you considered doing a labial mucosal biopsy on these patients, because this shows miniature Sjögren's syndrome in about 60 per cent. of patients with the fully expressed disease. It would be interesting to know whether patients with KCS alone had this lesion in their oral mucosa.

DR. GUMPEL There were a number of other investigations I should also have liked to do in the whole group, but because they are a fairly unusual population they are notably reluctant to submit to further medical attention or investigation. I propose, however, to investigate this group once again.

Ehlers-Danlos Syndrome. By P. BEIGHTON (*St. Thomas's Hospital*)

The Ehlers-Danlos syndrome is a genetically-determined disorder of connective tissue, characterized by hypermobile joints, hyperextensible skin, and a tendency for the skin to split on minor trauma with the formation of wide gaping scars. The condition is rare and about 300

cases have so far been recorded in the world literature.

During a recent survey in Southern England 100 cases have been examined and the following significant facts have emerged:

(1) The syndrome is probably composed of five separate entities which are clinically recognizable. The importance of these is that one of them is lethal, with a high incidence of sudden death, one is associated with many minor complications, and one is transmitted as an X-linked trait. The implication of this last fact is that this particular variety of the Ehlers-Danlos syndrome must be a completely separate condition.

(2) It has become apparent that musculoskeletal disorders occur generally in the Ehlers-Danlos syndrome. Among these are joint dislocations and subluxations, thoracic abnormality, and spinal deformity.

(3) Biochemical, haematological, chromosome, and genetic linkage investigations have been carried out.

Discussion

MR. A. P. BARABAS (*Postgraduate Medical School*) I should like to congratulate Dr. Beighton on this most thorough study of a large group of Ehlers-Danlos patients. In 1967 I examined 27 patients in the north of England with the same syndrome and it may be of interest to compare my findings with his. My classification basically agrees with that of Dr. Beighton. His 'gravis' group, the severely affected ones, I call the 'classical'. I have seen three families in his less severely affected 'mitis' group and they all had varicose veins. This may have happened by chance, but at the time I called the group the 'varicose' type. I have not seen any X-linked families, but I have observed one family which could be classified as 'benign hypermobile'. My main interest has been in the 'arterial' subjects which I think correspond to Dr. Beighton's 'ecchymotic' group. I think this is the most important group because in my series lethal complications occurred exclusively amongst the 'arterial' cases. I should like to ask Dr. Beighton, in view of the entirely different prognosis and also the different clinical and diagnostic picture, whether he would not agree to call the 'arterial' or 'ecchymotic' type a completely different disease? I think there would be practical advantages in this.

DR. BEIGHTON Yes, I think Mr. Barabas is quite right in this. Patients with the arterial or ecchymotic type of condition are clinically recognizable. They have thin, pale skin, with a very, very prominent venus plexus, their bleeding tendency is enormous, their scars tend to be darkly pigmented, and they are clinically very different, with a very high risk of the serious complications of dissected aorta, perforated gut, or ruptured arteries. Some time ago Mr. Barabas proposed (*Proc. roy. Soc. Med.* (1969), 62, 735) that this condition should be known as Sack's syndrome, as some years ago Sack described a 'status disvascularis', and I think this is a very reasonable suggestion. It must also be made perfectly clear that, although these lethal complications have a very high incidence in these clinically recognizable patients, those